such compounds has been described in infants (*3*) and in offspring of rhesus monkeys (*4*), as exemplified by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). For example, the half-life for nonmetabolic elimination of TCDD has been calculated to be 0.42 years in newborns, which is substantially shorter than in adults (*3*). From TCDD data collected over more than 15 years following the Seveso incident (*5*), it is obvious that the half-life is shorter in infants and increases significantly with age.

Although the amount of TCDD in the organism is a function of uptake and elimination, the resulting tissue concentrations are also functions of the body and tissue volumes. The fast growth in the first years of life leads to a "thinning" of the TCDD tissue concentrations (*3,6*). Although the relatively fast half-life, together with the "thinning" effect, are insufficient to prevent an increase of TCDD tissue concentrations during nursing, after weaning, both growth-related dilution and elimination from the body result in a fast decrease in these concentrations. In fact, TCDD concentrations in tissues of babies breast-fed for up to 6 months can reach values in the lower range of adults, but the concentrations decline rather quickly, reaching values comparable to nonbreast-fed children at about 5 years of age (*3*). Importantly, these results are based on general assumptions related to the class of compounds described as lipophilic, nonwater soluble, nonvolatile, nonprotein bound, and either slowly metabolized or not metabolized; therefore, these results should be valid not only for TCDD but for all compounds meeting this description (*3*).

In conclusion, based on the current scientific literature, even relatively high TCDD concentrations that might be reached after 6 months of nursing do not appear to lead to a raised lifetime value. Comparing intake from breast-feeding with cumulative long-term intake may result in misleading perceptions about health risks associated with intake of TCDD and congeners.

Judy S. LaKind
LaKind Associates, LLC
Catonsville, Maryland
E-mail: judy@jesse.mts.jhu.edu

Johannes G. Filser
GSF Forschungszentrum fur
Umwelt und Gesundheit GmbH
Neuherberg, Germany

References and Notes:

1. Patandin S, Dagnelie PC, Mulder PGH, Op de Coul E, van der Veen JE, Weisglas-Kuperus N, Sauer PJJ. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: a comparison between breast-feeding, toddler, and long-term exposure. Environ Health Perspect 107:45–51 (1999).
2. LaKind JS, et al. Unpublished data.
3. Kreuzer PE, Csanády GA, Baur C, Kessler W, Päpke O, Greim H, Filser JG. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and congeners in infants. A toxicokinetic model of human lifetime body burden by TCDD with special emphasis on its uptake by nutrition. Arch Toxicol 71(6):383–400 (1997).
4. Bowman RE, Tong HY, Gross ML, Monson SJ, Weerasinghe NCA. Controlled exposure of female rhesus monkeys to 2,3,7,8-TCDD: concentrations of TCDD in fat of offspring, and its decline over time. Chemosphere 20:1199–1202 (1990).
5. Mocarelli P, et al. Unpublished data.
6. Ayotte P, Dewailly E, Bruneau S, Careau H, Vezina A. Arctic air pollution and human health: what effects should be expected? Sci Total Environ 160/161: 529–537 (1995).

Patandin's Response

We would like to respond to LaKind and Filser's comments about our paper that was published in *EHP* (*1*).

LaKind and Filser emphasized that tissue concentrations of TCDD and related compounds are important when assessing potential adverse effects, rather than assessing long-term dietary intake only. We agree with them; however, long-term dietary intake is an important part of exposure assessment. In our paper we mainly focused on the polychlorinated biphenyl (PCB) and dioxin (polychlorinated dibenzodioxin and furan; PCDD/PCDF) intake during different periods in life. Over 90% of exposure to PCBs and dioxins in the general population is from oral intake. We compared the intake of toxic equivalents (TEQs) during breast-feeding (0–1 year of age), after weaning (e.g., preschool years; 1–5 years of age), and until adulthood (6–25 years of age). We also calculated the amount (percentage) of PCB/dioxin TEQ intake during a 6-month period of breast-feeding and its effect on the total cumulative intake until adulthood (25 years).

Although some model calculations of PCB/dioxin body burden and infant exposure through breast milk have been published (*2,3*), the cumulated PCB/dioxin intake from infancy until adulthood had not been quantitatively assessed. The cumulated intake as calculated in this study is not identical to body burden because losses by excretion and metabolism by the liver, as well as different half-lives of different PCB and dioxin congeners, are not taken into account (*1*). We calculated the total mean intake of PCBs/dioxins over a 25-year period in subjects who were either formula-fed or breast-fed for 3 and 6 months during infancy.

LaKind and Filser emphasized the thinning effect in infants during growth and the shorter half-lives reported for TCDD in infants. The dilution effect of PCBs and dioxins in the growing infant is a known phenomenon (*4,5*). This dilution effect is also found in older adults when the increase of PCB/dioxin tissue concentration is lower than expected because of the increase of total body fat with age (*2*).

In a previous publication (*6*), we presented the sum PCB levels (IUPAC numbers 118, 138, 153, and 180) measured in the plasma of 42-month-old children who were either breast-fed or formula-fed during infancy. The PCB levels measured at 42 months of age were strongly related ($r = 0.63$) to the period of breast-feeding and negatively associated with total body fat (percentage) and body weight. Preschool children who were breast-fed as infants have PCB body burdens that are primarily dictated by their lactational PCB exposures. The negative relationship with plasma PCB concentration and body fat percentage is most likely explained by the fact that PCBs and related compounds are distributed over all fat-containing components in the body, especially adipose tissue (diluted). Given a higher growth rate as well as this dilution effect, a shorter half-life has been reported for PCBs and dioxins in young children (*4,5*). Despite this rapid growth and shorter half-life, breast-fed infants reach PCB and dioxin levels as high as their mothers (adults) (*6*).

According to LaKind and Filser, the high TCDD tissue concentration after 6 months of breast-feeding does not give an increased lifetime value for TCDD body burden. This still needs to be investigated more thoroughly. Model calculations presented by Ayotte (*7*) show that body burden in breast-fed infants are relevant for the childhood years, but not for periods beyond 20–30 years of age. However, Smith (*8*) suggested that an infant breast-fed for 12 months would receive approximately 10% of the cumulative exposure dose per body weight that would be received by an adult with 50 years of exposure. During childhood, the body burden is raised by lactational PCB/dioxin exposure (*3,6*). At 25 years of age, the PCB/dioxin body burden could be higher due to breast-feeding for 6 months. We reported (*1*) that 6 months of breast-feeding contributes to over 10% of the cumulative dietary intake until 25 years of age. This amount of PCB/dioxin intake during 6 months of breast-feeding is not negligible and certainly will not result in misleading perceptions about health risk assessment. In this paper (*1*), we tried to give more quantitative information about the dietary intake and several body burden calculations. We want to emphasize that although PCB/dioxin accumulation in the infant's body is a disadvantage, there are numerous advantages of breast-feeding on the general development of infants; therefore, we do not encourage shortening the lactation period in the general population (*1,9*).

Svati Patandin
Department of Pediatrics
Sophia Children's Hospital
Rotterdam, The Netherlands
E-mail: ashrufpatandin@wanadoo.nl

References and Notes

1. Patandin S, Dagnelie PC, Mulder PGH, Op de Coul E, van der Veen JE, Weisglas-Kuperus N, Sauer PJJ. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: a comparison between breast-feeding, toddler and long-term exposure. Environ Health Perspect 107:45–51 (1999).
2. Duarte-Davidson R, Jones KC. Polychlorinated biphenyls (PCBs) in the UK population: estimated intake, exposure and body burden. Sci Total Environ 151(2):131–52 (1994).
3. Haschke F, Male C, Pietschnig B. Infant exposure to PCDDs and PCDFs through breast milk and an approach to calculate body burden. Toxic Subst J 12:227–236 (1992).
4. Yakushiji T, Watanabe I, Kuwabara K, Tanaka R, Kashimoto T, Kunita N, Hara I. Rate of decrease and half-life of polychlorinated biphenyls (PCBs) in the blood of mothers and their children occupationally exposed to PCBs. Arch Environ Contam Toxicol 13(3):341–345 (1984).
5. Ryan JJ, Hsu CC, Boyle MJ, Guo YL. Blood serum levels of PCDFs and PCBs in Yu-Cheng children peri-natally exposed to a toxic rice oil. Chemosphere 29(6):1263–1278 (1994).
6. Patandin S, Weisglas-Kuperus N, de Ridder MAJ, Koopman-Esseboom C, van Staveren WA, van der Paauw CG, Sauer PJJ. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy Am J Public Health 87:1711–1714 (1997).
7. Ayotte P, Carrier G, Dewailly E. Health risk assessment for Inuit new-borns exposed to dioxin-like compounds through breast-feeding. Chemosphere 32(3):531–542 (1996).
8. Smith AH. Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions. Risk Anal 7(3):347–353 (1987).
9. Patandin S, Lanting CI, Mulder PGH, Boersma ER, Sauer PJJ, Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33-41 (1999).

An Epidemic of Complex Dysmorphologic Syndromes in Southeast Spain?

I am a pediatrician at the Poniente Regional Hospital in El Ejido (Almeria), Spain. This hospital, which opened in 1995, offers specialized health care to the 150,000 inhabitants residing in El Poniente, a Mediterranean coast area located in the southeast of Spain. In the last 4 months I have diagnosed two newborns from this area who are affected by extremely rare dysmorphologic syndromes: *a*) a velocardiofacial syndrome and *b*) a complex polymalformation including facial dysmorphy and polysyndactilia in hands and feet associated with 2/8 translocation; neither child had familiar antecedents. Surprised by this uncommon geographical and temporal cluster (in the Poniente area there are only 2,000 newborns/year), I reexamined the cases of newborns affected by rare dysmorphologic syndromes that I previously diagnosed in this area. Some of these cases have been published (*1–6*) because each case involves a very rare disease. Below, I describe 11 cases (including the two cases described above):

- Four cases with velocardiofacial syndrome, which were diagnosed in the preceeding 5 years. After reviewing the international literature (via Medline; National Library of Medicine, Bethesda, MD), I only found 100 cases described in the world.
- Two cases of Jarcho-Levin syndrome (from a whole of 73 recorded in the reviewed literature).
- One case with 11q(-) syndrome (there are only 30 well-documented cases in the world).
- One case with 18q syndrome (< 100 cases described). Our case was also associated with a familiar genetic abnormality (trans 1-18 in both the mother and the sister).
- One case of atypical Klinefelter syndrome (48XXYY) (only 74 cases found in the literature).
- One case with cerebral–rib–mandible syndrome, which includes multiple vertebral and rib defects, micrognathia, glossoptosis, palatal anomalies, and slow physical and psychomotor growth.
- One case of translocation (t 2:8 q32-q21), which was mentioned above.

Assuming that no population-based incidence data are available, I think that this case–series constitutes an unusual geographic (the Poniente area) and temporal (the last 10 years) clustering of extremely scarce dysmorphologic syndromes that cannot be explained only by chance. Environmental factors may account for the observed aggregation. The teratogenic and mutagenic effects of some chemicals have been recognized for years. People living in the Poniente area are highly exposed to pesticides because of intensive farming activities. There are two main reasons to draw special attention to the etiologic role of agrochemical exposure.

First, there is an extremely high exposure rate to these substances in our area. Since the 1960s, intensive agriculture in greenhouses has expanded in southern Spain, close to the Mediterranean Sea. Approximately 40,000 hectares of plastic greenhouses are now located in the Poniente area, which represents the largest area devoted to this type of farming in Europe (*7*). This intensive cultivation is protected against pests by the use of large amounts of pesticides, frequently used without the basic required safety measures. Moreover, acute intoxication by pesticides is one of the most well-documented health problems in our area. In addition, exposure to agrochemicals in women working in intensive agriculture presents a special situation because bioaccumulated pesticides can be mobilized during pregnancy and lactation.

Second, the endocrine-disrupting effects of pesticides in several animal species has been well documented (*8*). Some hypotheses suggest that this effect may also extend to humans (*9*). Because the exposure to these substances in the Poniente area is very high, the implications of their effects on human health is a matter of great concern. But this is not a local problem because pesticides are commonly used all over the world.

It is urgent that we investigate the possible causal links between pesticides and health effects, particularly those affecting human reproduction and embrionic and fetal development. Are similar dysmorphologic syndromes being observed in other farming areas? Pesticide use and human exposure is a worldwide matter.

Francisco Cañabate Reche
Servicio De Pediatria
Hospital De Poniente
Almeria, España
E-mail: canabat@larural.es

References and Notes

1. Cañabate Reche F, Gonzalez-Ripoll Garzon M, Martin Gonzalez M, Lopez Muñoz J. Sindrome de Jarcho-Levin: presentación de tres casos. Malformaciones extraesqueléticas asociadas. An Esp Pediatr 38:54–56 (1993).
2. Garcia Peñas JJ, Cañabate Reche F, Gonzalez-Ripoll Garzon M, Lopez Muñoz J. Sindrome 18 q(-): presentación de un caso y estudio genético familiar. Rev Esp Pediatr 49:176–178 (1993).
3. Cañabate Reche F, Gonzalez-Ripoll Garzon M, Garcia Peñas JJ, Garcia Gonzalez JM, Espin Galvez J, Martin Gonzalez M, Lopez Muñoz J. Sindrome 11 q(-): presentación de un nuevo case. An Esp Pediatr 38:562–563 (1993).
4. Cañabate Reche F, Gonzalez-Ripoll Garzon M, Garcia Peñas JJ, Ramos Lizana J, Martin Gonzalez M, Garcia Gonzalez JM, Lopez Muñoz J. Sindrome de Klinefelter atipico: 48 XXYY: presentatación de un case de diagnóstico precoz. Rev Est Pediatr 51:575–578 (1995).
5. Cañabate Reche F, Garcia Peñas JJ, Gonzalez-Ripoll Garzon M, Ruiz Gomez C, Lopez Muñoz J. Sindrome velocardiofacial. Evolución natural de 4 casos. Malformaciones asociadas. An Esp Pediatr 45:205–208 (1996).
6. Ortiz Lopez I, Cañabate Reche F, Sanchez Vazquez AR, Garcia Lopez MA, Ramos Lizana J, Lopez Muñoz J. Del fenotipo al diagnóstico: sindrome cerebro-costo-mandibular [abstract]. XXVI Congreso de la A.E.P. Santiago de Compostela. An Esp Pediatr 84:92 (1996).
7. Olea N, Olea-Serrano MF. Oestrogens and the environment. Eur J Cancer Prevention 5:491–496 (1996).
8. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:378–384 (1993).
9. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jégou B, Jensen TK, Jouannet P, Keiding N, et al. Male Reproductive Health and Environmental Chemicals with Estrogenic Effects. Miljoeprojekt No. 290. Copenhagen:Ministry of Environment and Energy, Danish Environmental Protection Agency, 1995.